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DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=ADJ			
L7	l6 and l2	29	L7
L6	l5 same l3	119	L6
L5	inhibit$5	659379	L5
L4	l2 and l3	42	L4
L3	(dipeptidyl peptidase iv)	219	L3
L2	hyperglycemi$6	3580	L2
L1	(aminoacyl-thiazolidide) or (alanyl-pyrolidide) or (isoleucyl-thiazolidide) n-valyl-propyl or (o-benzoyl hydroxyamine)	1	L1

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L7: Entry 20 of 29 File: USPT Aug 14, 2001

DOCUMENT-IDENTIFIER: US 6274608 B1
TITLE: Compounds, their preparation and use

Brief Summary Paragraph Right (5):
In the diabetic, tissues dependant on insulin are unable to assimilate glucose normally (insulin resistance), the result being an accumulation of glucose within the blood (hyperglycemia). Type II diabetes typically afflicts people over 40, and obesity is often a contributing factor. Regulation of diet and exercise can reduce to some extent the problems associated with NIDDM, but commonly insulin therapy or other oral hypoglycemic agents are the treatments of choice.

Brief Summary Paragraph Right (7):
More recently, a class of compounds termed thiazolidinediones (e.g., ciglitazone, pioglitazone, englitazone, troglitazone and BRL 49653) have been shown to reduce hyperglycemia by promoting insulin action without additional insulin secretion, and without causing undesirable hypoglycemia, even at elevated doses. Their effect is proposed to be a result of agonism at the PPAR receptor.

Brief Summary Paragraph Right (8):
Even more recently, it has been reported that RXR agonists such as LGD 1069 and LG 100268 activate RXR/PPAR heterodimers, causing reduction in glucose, insulin and triglyceride levels in ob/ob and db/db mice (Mukherjee et al., Nature 1997, 386, 407410, Heyman and Mukherjee WO 97/10819). This effect is due to activation at the RXR part of the heterodimer. In turn these RXR/PPAR heterodimers can also be activated by PPAR agonists (e.g., thiazolidinediones) to give a similar effect, and it has been shown that at submaximal levels of either the RXR or PPAR agonist, addition of the complimentary agonist provides an additive and possibly synergistic response, and results in enhanced transcription and subsequently additional lowering of hyperglycemia, hyperinsulinemia and hypertriglyceridemia. It has therefore been proposed that compounds acting as agonists at both the RXR and PPAR receptors can be used as insulin sensitizers for the treatment of Type II diabetes and related symptoms.

Brief Summary Paragraph Right (13):
A number of compounds have been reported to be useful in the treatment of hyperglycemia, hyperlipidemia and hypercholesterolemia (U.S. Pat. No. 5,306,726, PCT Publications nos. WO91/19702, WO 95/03038, WO 96104260, WO 94/13650, WO 94/01420, WO 97/36579, WO 97/25042, WO 95/17394, WO 99108501, WO 99/19313 and WO 99/16758).

Brief Summary Paragraph Right (45):
In still another aspect, the present compounds are useful for the treatment and/or prophylaxis of insulin resistance (Type 2 diabetes), impaired glucose tolerance, dyslipidemia, disorders related to Syndrome X such as hypertension, obesity, insulin resistance, hyperglycemia, atherosclerosis, hyperlipidemia, coronary artery disease, myocardial ischemia and other cardiovascular disorders.

Brief Summary Paragraph Right (81):
The orally active hypoglycemic agents preferably comprise sulphonylureas, biguanides, meglitinides, glucosidase inhibitors, glucagon antagonists such as those disclosed in WO 99/01423 to Novo Nordisk AIS and Agouron Pharmaceuticals, Inc., GLP-1 agonists, potassium channel openers such as those disclosed in WO 97126265 and WO 99/03861 to Novo Nordisk A/S which are incorporated herein by reference, DPP-IV (dipeptidyl peptidase-IV) inhibitors, inhibitors of hepatic enzymes involved in stimulation of

gluconeogenesis and/or glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents as HMG CoA inhibitors (statins), compounds lowering food intake, and agents acting on the ATP-dependent potassium channel of the .beta.-cells.

L7: Entry 23 of 29 File: USPT Jan 6, 1998

DOCUMENT-IDENTIFIER: US 5705483 A
TITLE: Glucagon-like insulinotropic peptides, compositions and methods

Brief Summary Paragraph Right (3):
The human hormone glucagon is a 29-amino acid peptide hormone produced in the A-cells of the pancreas. The hormone belongs to a multi-gene family of structurally related peptides that include secretin, gastric inhibitory peptide, vasoactive intestinal peptide and glicentin. These peptides variously regulate carbohydrate metabolism, gastrointestinal mobility and secretory processing. The principal recognized actions of pancreatic glucagon, however, are to promote hepatic glycogenolysis and glyconeogenesis, resulting in an elevation of blood sugar levels. In this regard, the actions of glucagon are counter regulatory to those of insulin and may contribute to the hyperglycemia that accompanies Diabetes mellitus [(Lund, P. K., et el., Proc. Natl. Aced. Sci. U.S.A., 79:345-349 (1982)].

Brief Summary Paragraph Right (10):
More particularly, the fundamental defects identified as causing hyperglycemia in maturity onset diabetes are impaired secretion of endogenous insulin and resistance to the effects of insulin by muscle and liver [Galloway, J. S., Diabetes Care, 13:1209-1239, (1990)]. The latter defect results in excessive production of glucose from the liver. Thus, whereas a normal individual releases glucose at the rate of approximately 2 mg/kg/minute, in patients with maturity onset diabetes, this amount usually exceeds 2.5 mg/kg/minute resulting in a net excess of at least 70 grams of glucose per 24 hours. The fact that there exists exceedingly high correlations between hepatic glucose production, the fasting blood glucose and overall metabolic control as indicated by glycohemoglobin measurements [Galloway, J. A., supra; and Galloway, J. A., et al., Clin. Therap., 12:460=472 (1990)], it is readily apparent that control of the fasting blood glucose is a sine quo non for achieving overall normalization of metabolism sufficient to prevent the complication of hyperglycemia. In view of the fact that present forms of insulin rarely normalize hepatic glucose production without producing significant hyperinsulinemia and hypoglycemia (Galloway, J. A., and Galloway, J. A., et al., Supra) alternative approaches are needed.

Brief Summary Paragraph Right (23):
In addition to protected forms in which both amino and carboxy groups possess appropriate protecting groups, the term "protected" also refers to those GLP-1 molecules in which the activity of dipeptidyl-peptidase IV is resisted or inhibited [see, e.g., Mentlein, R., et al., Eur. J. Biochem., 214:829-835 (1993)]. In addition to GLP-1(7-36)NH.sub.2, molecules which are protected from the activity of DPP IV are preferred, and Gly.sup.8 -GLP-1(7-36)NH.sub.2, Val.sup.8 -GLP-1(7-37)OH, .alpha.-methly-Ala.sup.8 -GLP-1(7-36)NH.sub.2, and Gly.sup.8 -Gln.sup.21 -GLP-1(7-37)OH are more preferred.

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L7: Entry 22 of 29 File: USPT Nov 2, 1999

DOCUMENT-IDENTIFIER: US 5977071 A
TITLE: Glucagon-like insulinotropic peptides, compositions and methods

Brief Summary Paragraph Right (3):
The human hormone glucagon is a 29-amino acid peptide hormone produced in the A-cells of the pancreas. The hormone belongs to a multi-gene family of structurally related peptides that include secretin, gastric inhibitory peptide, vasoactive intestinal peptide and glicentin. These peptides variously regulate carbohydrate metabolism, gastrointestinal mobility and secretory processing. The principal recognized actions of pancreatic glucagon, however, are to promote hepatic glycogenolysis and glyconeogenesis, resulting in an elevation of blood sugar levels. In this regard, the actions of glucagon are counter regulatory to those of insulin and may contribute to the hyperglycemia that accompanies Diabetes mellitus [(Lund, P. K., et al., Proc. Natl. Acad. Sci. U.S.A., 79:345-349 (1982)].

Brief Summary Paragraph Right (10):
More particularly, the fundamental defects identified as causing hyperglycemia in maturity onset diabetes are impaired secretion of endogenous insulin and resistance to the effects of insulin by muscle and liver [Galloway, J. S., Diabetes Care, 13:1209-1239, (1990)]. The latter defect results in excessive production of glucose from the liver. Thus, whereas a normal individual releases glucose at the rate of approximately 2 mg/kg/minute, in patients with maturity onset diabetes, this amount usually exceeds 2.5 mg/kg/minute resulting in a net excess of at least 70 grams of glucose per 24 hours. The fact that there exists exceedingly high correlations between hepatic glucose production, the fasting blood glucose and overall metabolic control as indicated by glycohemoglobin measurements [Galloway, J. A., supra; and Galloway, J. A., et al., Clin. Therap., 12:460-472 (1990)], it is readily apparent that control of the fasting blood glucose is a sine quo non for achieving overall normalization of metabolism sufficient to prevent the complication of hyperglycemia. In view of the fact that present forms of insulin rarely normalize hepatic glucose production without producing significant hyperinsulinemia and hypoglycemia (Galloway, J. A., and Galloway, J. A., et al., supra) alternative approaches are needed.

Brief Summary Paragraph Right (23):
In addition to protected forms in which both amino and carboxy groups possess appropriate protecting groups, the term "protected" also refers to those GLP-1 molecules in which the activity of dipeptidyl-peptidase IV is resisted or inhibited [see, e.g., Mentlein, R., et al., Eur. J. Biochem., 214:829-835 (1993)]. In addition to GLP-1(7-36)NH.sub.2, molecules which are protected from the activity of DPP IV are preferred, and Gly.sup.8 -GLP-1(7-36)NH.sub.2, Val.sup.8 -GLP-1(7-37)OH, .alpha.-methly-Ala.sup.8 -GLP-1(7-36)NH.sub.2, and Gly.sup.8 -Gln.sup.21 -GLP-1(7-37)OH are more preferred.

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L7: Entry 15 of 29 File: USPT May 14, 2002

DOCUMENT-IDENTIFIER: US 6388053 B1
TITLE: Glucagon-like insulinotropic peptides, compositions and methods

Brief Summary Paragraph Right (3):
The human hormone glucagon is a 29-amino acid peptide hormone produced in the A-cells of the pancreas. The hormone belongs to a multi-gene family of structurally related peptides that include secretin, gastric inhibitory peptide, vasoactive intestinal peptide and glicentin. These peptides variously regulate carbohydrate metabolism, gastrointestinal mobility and secretory processing. The principal recognized actions of pancreatic glucagon, however, are to promote hepatic glycogenolysis and glyconeogenesis, resulting in an elevation of blood sugar levels. In this regard, the actions of glucagon are counter regulatory to those of insulin and may contribute to the hyperglycemia that accompanies Diabetes mellitus [(Lund, P. K., et al., Proc. Natl. Acad. Sci. U.S.A., 79:345-349 (1982)].

Brief Summary Paragraph Right (10):
More particularly, the fundamental defects identified as causing hyperglycemia in maturity onset diabetes are impaired secretion of endogenous insulin and resistance to the effects of insulin by muscle and liver [Galloway, J. S., Diabetes Care, 13:1209-1239, (1990)]. The latter defect results in excessive production of glucose from the liver. Thus, whereas a normal individual releases glucose at the rate of approximately 2 mg/kg/minute, in patients with maturity onset diabetes, this amount usually exceeds 2.5 mg/kg/minute resulting in a net excess of at least 70 grams of glucose per 24 hours. The fact that there exists exceedingly high correlations between hepatic glucose production, the fasting blood glucose and overall metabolic control as indicated by glycohemoglobin measurements [Galloway, J. A., supra; and Galloway, J. A., et al., Clin. Therap., 12:460-472 (1990)], it is readily apparent that control of the fasting blood glucose is a sine quo non for achieving overall normalization of metabolism sufficient to prevent the complication of hyperglycemia. In view of the fact that present forms of insulin rarely normalize hepatic glucose production without producing significant hyperinsulinemia and hypoglycemia (Galloway, J. A., and Galloway, J. A., et al., supra) alternative approaches are needed.

Brief Summary Paragraph Right (23):
In addition to protected forms in which both amino and carboxy groups possess appropriate protecting groups, the term "protected"also refers to those GLP-1 molecules in which the activity of dipeptidyl-peptidase IV is resisted or inhibited [see, e.g., Mentlein, R., et al., Eur. J. Biochem., 214:829-835 (1993)]. In addition to GLP-1(7-36)NH.sub.2, molecules which are protected from the activity of DPP IV are preferred, and Gly.sup.8 -GLP-1(7-36)NH.sub.2, Val.sup.8 -GLP-1(7-37)OH, .alpha.-methly-Ala.sup.8 -GLP-1(7-36)NH.sub.2, and Gly.sup.8 -Gln.sup.21 -GLP-1(7-37)OH are more preferred.

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 NEWS  7  Mar 22   TOXLIT no longer available
 NEWS  8  Mar 22   TRCTHERMO no longer available
 NEWS  9  Mar 28   US Provisional Priorities searched with P in CA/CAplus
                   and USPATFULL
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 NEWS 18  Apr 22   Federal Research in Progress (FEDRIP) now available
 NEWS 19  Jun 03   New e-mail delivery for search results now available
 NEWS 20  Jun 10   MEDLINE Reload
 NEWS 21  Jun 10   PCTFULL has been reloaded

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               AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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=> s alanyl-pyrolidide? or isoleucyl-thiazolidide? or n-valyl-prolyl? or (o-benzoyl hydroxylamine?) or aminoacyl-thiazolidide?
L1 15 ALANYL-PYROLIDIDE? OR ISOLEUCYL-THIAZOLIDIDE? OR N-VALYL-PROLYL? OR (O-BENZOYL HYDROXYLAMINE?) OR AMINOACYL-THIAZOLIDIDE?

=> dup rem l1
PROCESSING COMPLETED FOR L1
L2 14 DUP REM L1 (1 DUPLICATE REMOVED)

=> d 1-14 ab,bib

L2 ANSWER 1 OF 14 MEDLINE
AB In the CBA x DBA/2 mouse model, stress-triggered abortions are mediated by a Th1-like cytokine response of decidual lymphocytes. The factors that determine the cytokine pattern leading to abortion are currently unknown. Dipeptidyl Peptidase IV (DP IV) enhances Th1-cytokine responses and impairs the evolvement of a Th2 cytokine profile. The T-cell-activation antigen, CD26, possesses DP IV activity. The aim of the present study was to investigate the role of DP IV activity and CD26-positive decidual lymphocytes in murine stress-triggered abortions by inhibition of DP IV activity. DBA/2-mated CBA mice were stressed on day 5.5 of pregnancy and received daily injections of an inhibitor of DP IV activity, Ile-thiazolidide (20 micromol/kg). On day 13 of gestation, the animals were sacrificed and the percentage of implants and abortions documented. CD26-positive lymphocytes in spleen and uterine decidua and the intracellular cytokines interferon (IFN)-gamma and interleukin (IL)-10 were determined by flow cytometry. Stressed and nonstressed animals receiving an inactive stereoisomeric form were used as controls. In mice receiving the DP IV inhibitor, stress failed to boost the abortion rate (37.2% versus 13.6%, P < 0.01). IFN-gamma producing cells were increased in stressed animals, but returned to the baseline upon the inhibition of DP IV. The number of IL-10 producing cells was reduced in stressed animals, independent from DP IV inhibition.
AN 2001249247 MEDLINE
DN 21206358 PubMed ID: 11309152
TI Inhibition of dipeptidyl peptidase IV (DP IV, CD26) activity abrogates stress-induced, cytokine-mediated murine abortions.
AU Hildebrandt M; Arck P C; Kruber S; Demuth H U; Reutter W; Klapp B F
CS Medizinische Klinik m.S. Psychosomatik, Charite, Humboldt-Universitat zu

Berlin, Germany.. hildebra@charite.de
SO SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (2001 May) 53 (5) 449-54.
Journal code: 0323767. ISSN: 0300-9475.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200105
ED Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010510

L2 ANSWER 2 OF 14 MEDLINE
AB Glucagon is a 29-amino acid polypeptide released from pancreatic islet alpha-cells that acts to maintain euglycemia by stimulating hepatic glycogenolysis and gluconeogenesis. Despite its importance, there remains controversy about the mechanisms responsible for glucagon clearance in the body. In the current study, enzymatic metabolism of glucagon was assessed using sensitive mass spectrometric techniques to identify the molecular products. Incubation of glucagon with purified porcine dipeptidyl peptidase IV (DP IV) yielded sequential production of glucagon(3-29) and glucagon(5-29). In human serum, degradation to glucagon(3-29) was rapidly followed by N-terminal cyclization of glucagon, preventing further DP IV-mediated hydrolysis. Bioassay of glucagon, following incubation with purified DP IV or normal rat serum demonstrated a significant loss of hyperglycemic activity, while a similar incubation in DP IV-deficient rat serum did not show any loss of glucagon bioactivity. Degradation, monitored by mass spectrometry and bioassay, was blocked by the specific DP IV inhibitor, isoleucyl thiazolidine. These results identify DP IV as a primary enzyme involved in the degradation and inactivation of glucagon. These findings have important implications for the determination of glucagon levels in human plasma.
AN 2001136578 MEDLINE
DN 20564737 PubMed ID: 11111019
TI Metabolism of glucagon by dipeptidyl peptidase IV (CD26).
AU Pospisilik J A; Hinke S A; Pederson R A; Hoffmann T; Rosche F; Schlenzig D; Glund K; Heiser U; McIntosh C H; Demuth H
CS Department of Physiology, University of British Columbia, British Columbia, V6T 1Z3, Vancouver, Canada.
SO REGULATORY PEPTIDES, (2001 Jan 12) 96 (3) 133-41.
Journal code: 8100479. ISSN: 0167-0115.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200103
ED Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010301

L2 ANSWER 3 OF 14 CA COPYRIGHT 2002 ACS
AB A method is provided with which, by inhibiting dipeptidyl peptidase IV (DPIV) and/or DPIV-analogous enzyme activity in the blood of a mammal, the endogenous (or addnl. exogenously administered) glycogenolytic peptide glucagon (or analogs thereof) degraded by DPIV and DPIV-analogous enzymes is reduced, and thus the decrease in concn. of this peptide hormone and/or

its analogs is retarded. Through the effect obtained with the DPIV inhibitors, there is increased stability of the (endogenous or exogenous) glucagon/glucagon analogs, thereby increasing glycogenolytic stimulation of glucagon receptors, in particular in liver cells, changing the duration of effectiveness of the body's glucagon, involving a stimulation of the carbohydrate metab. As result, the blood sugar level rises over the glucose concn. characteristic of hypoglycemia in the serum of the treated organism. Thus, metabolic anomalies, e.g. hypoglycemic conditions, which are the result of decreased glucose concns. in the blood., are prevented and/or ameliorated. The method of the invention represents a new approach for increasing endogenous blood glucose concn. It is simple, and com. useful. The effect of DPIV inhibitor **isoleucyl thiazolidide** is presented.

AN 132:117551 CA
TI Procedure for the increase of the blood glucose level in mammals
IN Demuth, Hans-Ulrich; Hoffmann, Torsten; Kuhn-Wache, Kerstin; Rosche, Fred
PA Probiodrug Gesellschaft fur Arzneimittelforschung m.b.H., Germany
SO Ger. Offen., 8 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19834591	A1	20000203	DE 1998-19834591	19980731
	EP 995440	A1	20000426	EP 1999-115236	19990802
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	US 6319893	B1	20011120	US 1999-365404	19990802
	US 2002071838	A1	20020613	US 2001-682968	20011102
PRAI	DE 1998-19834591	A	19980731		
	US 1999-365404	A3	19990802		

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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 14 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:239685 BIOSIS
DN PREV200100239685
TI DP IV-inhibitors: Potential antidiabetic drugs.
AU Schlenzig, D. (1); Kruber, S. (1); White, H. A.; Pederson, R. A.; Demuth, H.-U. (1)
CS (1) Probiodrug Gesellschaft fuer Arzneimittelforschung mbH, Weinbergweg 22, 06120, Halle Germany
SO Fields, Gregg B.; Tam, James P.; Barany, George. (2000) pp. 224-226. Peptides for the new millennium. print.
Publisher: Kluwer Academic Publishers 3300 AA, Dordrecht, Netherlands.
Meeting Info.: 16th American Peptide Symposium Minneapolis, MI, USA June 26-July 01, 1999
ISBN: 0-7923-6445-7 (cloth).
DT Book; Conference
LA English
SL English

L2 ANSWER 5 OF 14 MEDLINE
AB Dipeptidyl peptidase IV is known to be involved, due to both hydrolytic and non-hydrolytic mechanisms, in various cell functions of normal and cancer cells as well. In this report dipeptidyl peptidase IV substrate and

pH preferences, some inhibition parameters, freezing/thawing sensitivity and stability against hydrolysis by trypsin were studied in C6 rat glioma cells. Our results confirmed substantial heterogeneity of dipeptidyl peptidase IV population. Such observation is important to avoid methodological artifacts and to decrease risk of misinterpretations in biological studies.

AN 2000439421 MEDLINE
DN 20439658 PubMed ID: 10985474
TI Heterogeneity of dipeptidyl peptidase IV from C6 rat glioma cells.
AU Malik R; Vlasicova L; Kadlecova L; Sedo A
CS 1st Department of Medical Chemistry and Biochemistry, 1st Faculty of Medicine, Charles University, Prague 2, Czech Republic.
SO NEOPLASMA, (2000) 47 (2) 96-9.
Journal code: 0377266. ISSN: 0028-2685.
CY Slovakia
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200009
ED Entered STN: 20000928
Last Updated on STN: 20000928
Entered Medline: 20000915

L2 ANSWER 6 OF 14 MEDLINE
AN 1999424399 MEDLINE
DN 99424399 PubMed ID: 10494612
TI [Inhibition of incretin degradation--a new therapy principle for treatment
of type 2 diabetes?].
Inhibition der Inkretindegradation--ein neues Therapieprinzip zur Behandlung des Typ-2-Diabetes?.
AU Gallwitz B; Schmidt W E
CS Medizinische Klinik I, St.-Josef-Hospital, Ruhr-Universitat Bochum.
SO ZEITSCHRIFT FUR GASTROENTEROLOGIE, (1999 Aug) 37 (8) 755-60.
Journal code: 0033370. ISSN: 0044-2771.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA German
FS Priority Journals
EM 199911
ED Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991119

L2 ANSWER 7 OF 14 MEDLINE
AB The incretins glucose-dependent insulinotropic polypeptide (GIP1-42) and truncated forms of glucagon-like peptide-1 (GLP-1) are hormones released from the gut in response to ingested nutrients, which act on the pancreas to potentiate glucose-induced insulin secretion. These hormones are rapidly inactivated by the circulating enzyme dipeptidyl peptidase IV ([DPIV] CD26). This study describes the effect on glucose tolerance and insulin secretion of inhibiting endogenous DPIV in the rat using Ile-thiazolidide, a specific DPIV inhibitor. High-performance liquid chromatography (HPLC) analysis of plasma following in vivo administration of 125I-labeled peptides showed that inhibition of DPIV by about 70% prevented the degradation of 90.0% of injected 125I-GLP-17-36 after 5 minutes, while only 13.4% remained unhydrolyzed in rats not treated with the DPIV-inhibiting agent after only 2 minutes. Ile-thiazolidide treatment
also increased the circulating half-life of intact GLP-17-36 released in

response to intraduodenal (ID) glucose (as measured by N-terminal specific radioimmunoassay [RIA]). In addition, inhibition of DPIV in vivo resulted in an earlier increase and peak of plasma insulin and a more rapid clearance of blood glucose in response to ID glucose challenge. When considered with the HPLC data, these results suggest that the altered insulin profile is an incretin-mediated response. DPIV inhibition resulting in improved glucose tolerance may have therapeutic potential for the management of type 2 diabetes mellitus.

AN 1999191906 MEDLINE
DN 99191906 PubMed ID: 10094118
TI Improved glucose tolerance in rats treated with the dipeptidyl peptidase IV (CD26) inhibitor Ile-thiazolidide.
AU Pauly R P; Demuth H U; Rosche F; Schmidt J; White H A; Lynn F; McIntosh C H; Pederson R A
CS Department of Physiology, University of British Columbia, Vancouver, Canada.
SO METABOLISM: CLINICAL AND EXPERIMENTAL, (1999 Mar) 48 (3) 385-9. Journal code: 0375267. ISSN: 0026-0495.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199904
ED Entered STN: 19990426
Last Updated on STN: 19990426
Entered Medline: 19990413

L2 ANSWER 8 OF 14 CA COPYRIGHT 2002 ACS DUPLICATE 1
AB The conjugate addn. of N-BOC-**O-benzoyl hydroxylamine** catalyzed by NaH to chiral .alpha.,.beta.-unsatd. imide I gives protected benzoyloxyaminopropanoyl deriv. II. II undergoes cyclization on treatment with sodium or lithium bases to give aziridine-2-imide III in good yield and diastereoselectivity. When N-BOC-**O-benzoyl hydroxylamine** is deprotonated with stoichiometric lithium or sodium bases, the intermediate enolate resulting from 1,4-addn. to I spontaneously undergoes cyclization affording in a single step the N-BOC aziridine III in higher yield.
AN 129:175937 CA
TI Diastereoselective synthesis of 3'-unsubstituted N-Boc-aziridine from a readily available chiral .alpha.,.beta.-unsaturated imide
AU Cardillo, Giuliana; Gentilucci, Luca; Bastardas, Imma Ratera; Tolomelli, Alessandra
CS Dip. Chim. "G. Ciamician" and CSFM-CNR, Univ. Bologna, Bologna, 40126, Italy
SO Tetrahedron (1998), 54(28), 8217-8222
CODEN: TETRAB; ISSN: 0040-4020
PB Elsevier Science Ltd.
DT Journal
LA English
OS CASREACT 129:175937

L2 ANSWER 9 OF 14 MEDLINE
AB The hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP)-1 act on the pancreas to potentiate glucose-induced insulin secretion (enteroinsular axis). These hormones (incretins) are rapidly hydrolyzed by the circulating enzyme dipeptidyl

peptidase IV (DP IV) into biologically inactive NH2-terminally truncated fragments. This study describes the effect of inhibiting endogenous DP IV with a specific DP IV inhibitor, isoleucine thiazolidide (Ile-thiazolidide), on glucose tolerance and insulin secretion in the obese Zucker rat. In initial studies, the specificity of Ile-thiazolidide as an inhibitor of incretin degradation was determined using matrix-assisted laser desorption/ionization-time of flight mass spectrometry. These results showed that inhibiting DP IV activity with Ile-thiazolidide blocked the formation of NH2-terminally truncated GIP and GLP-1. Oral administration of Ile-thiazolidide resulted in rapid inhibition of circulating DP IV levels by 65% in obese and lean Zucker rats. Suppression of DP IV levels enhanced insulin secretion in both phenotypes with the most dramatic effect occurring in obese animals (150% increase in integrated insulin response vs. 27% increase in lean animals).

Ile-thiazolidide treatment improved glucose tolerance in both phenotypes and restored glucose tolerance to near-normal levels in obese animals. This was attributed to the glucose-lowering actions of increasing the circulating half-lives of the endogenously released incretins GIP and, particularly, GLP-1. This study suggests that drug manipulation of plasma incretin activity by inhibiting the enzyme DP IV is a valid therapeutic approach for lowering glucose levels in NIDDM and other disorders involving glucose intolerance.

AN 1998366885 MEDLINE
DN 98366885 PubMed ID: 9703325
TI Improved glucose tolerance in Zucker fatty rats by oral administration of the dipeptidyl peptidase IV inhibitor isoleucine thiazolidide.
AU Pederson R A; White H A; Schlenzig D; Pauly R P; McIntosh C H; Demuth H U
CS Department of Physiology, University of British Columbia, Vancouver, Canada.. pederson@unixg.ubc.ca
SO DIABETES, (1998 Aug) 47 (8) 1253-8.
Journal code: 0372763. ISSN: 0012-1797.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199809
ED Entered STN: 19980917
Last Updated on STN: 20000303
Entered Medline: 19980909

L2 ANSWER 10 OF 14 CA COPYRIGHT 2002 ACS
AB Administration of agents which lower the blood dipeptidyl peptidase IV activity decreases the degrdn. of the (endogenous or exogenous) insulinotropic peptides, (1-42)-gastric inhibitory polypeptide and (7-36)-glucagonlike peptide 1 amide, and consequently enhances the insulinotropic stimulation of integrin receptors on pancreatic islet cells, stimulates carbohydrate metab., and decreases the serum glucose level. Thus, **isoleucyl thiazolidide** (0.1 mg i.v.) administration to rats after intraduodenal administration of glucose dose-dependently lowered the blood glucose level.
AN 127:341803 CA
TI Method for lowering the blood glucose level in mammals
IN Demuth, Hans-Ulrich; Rosche, Fred; Schmidt, Joern; Pauly, Robert P.; Mclntosh, Christopher H. S.; Pederson, Ray A.
PA Hans-Knoell-Institut fuer Naturstoff-Forschung e.V., Germany
SO Ger. Offen., 7 pp.
CODEN: GWXXBX
DT Patent

LA German
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19616486	A1	19971030	DE 1996-19616486	19960425
	DE 19616486	C2	19990812		
	CA 2252576	AA	19971106	CA 1997-2252576	19970424
	WO 9740832	A1	19971106	WO 1997-DE820	19970424
	W: AU, CA, CN, JP, KR, MX, NZ, RU, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9730233	A1	19971119	AU 1997-30233	19970424
	AU 721477	B2	20000706		
	EP 896538	A1	19990217	EP 1997-924866	19970424
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	CN 1216468	A	19990512	CN 1997-194017	19970424
	EP 1084705	A2	20010321	EP 2000-119496	19970424
	EP 1084705	A3	20020515		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	AT 202705	E	20010715	AT 1997-924866	19970424
	JP 2001510442	T2	20010731	JP 1997-538453	19970424
	ES 2158562	T3	20010901	ES 1997-924866	19970424
	US 6303661	B1	20011016	US 1998-155833	19981006
PRAI	DE 1996-19616486	A	19960425		
	EP 1997-924866	A3	19970424		
	WO 1997-DE820	W	19970424		

L2 ANSWER 11 OF 14 CA COPYRIGHT 2002 ACS
AB The mechanism of inactivation of serine proteases by N-peptidyl-O-aroylhydroxylamines was studied by X-ray crystallog. Cocrystals of subtilisin Carlsberg inactivated with N-((tert-butoxycarbonyl)alanylprolylphenylalanyl)-O-nitrobenzoyl hydroxylamine were grown, and diffraction data to 1.8-.ANG. resoln. were obtained. The resulting electron d. maps clearly reveal that the .gamma.-oxygen of the catalytic serine forms a carbamate deriv. with the inhibitor. The peptide part of the inhibitor does not form the usual antiparallel .beta.-sheet in the P binding cleft but protrudes out of the active site and is stabilized by a network of water mols. These results, combined with kinetic characterization reported previously [Demuth, H.-U., Schoenlein, C., & Barth, A.(1989b) Biochim. Biophys. Acta 996, 19-22; Schmidt, C., Schmidt, R., & Demuth, H.-U. (1990) Peptides (Giralt, E., & Andreu, D., Eds.) ESCOM Science Publishers B.V., New York] support the existence of at least one intermediate between the formation of the Michaelis complex and the final product. The authors suggest a mechanism for the inactivation of subtilisin Carlsberg by N-((tert-butoxycarbonyl)alanylprolylphenylalanyl)-**O-benzoyl hydroxylamine** whereby a neg. charged Michaelis complex undergoes a Lossen rearrangement giving rise to an isocyanate intermediate that reacts with the side chain of the active site serine.
AN 121:128521 CA
TI Inactivation of Subtilisin Carlsberg by N-((tert-

Butoxycarbonyl)alanylprolylphenylalanyl)-**O-benzoyl Hydroxylamine**: Formation of a Covalent Enzyme-Inhibitor Linkage in the Form of a Carbamate Derivative
AU Steinmetz, Anke C. U.; Demuth, Hans-Ulrich; Ringe, Dagmar
CS Department of Biochemistry and Chemistry, Brandeis University, Waltham, MA, 02254, USA
SO Biochemistry (1994), 33(34), 10535-44
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English

L2 ANSWER 12 OF 14 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1975:201028 BIOSIS
DN BA60:31024
TI MECHANISM OF CYTOCHROME C PEROXIDASE EC-1.11.1.5 **O BENZOYL HYDROXYLAMINE** AS AN ANALOG OF HYDROGEN PER OXIDE.
AU COULSON A F W; YONETANI T
SO BIOCHEMISTRY, (1975) 14 (11), 2389-2396.
CODEN: BICHAW. ISSN: 0006-2960.
FS BA; OLD
LA Unavailable

L2 ANSWER 13 OF 14 CA COPYRIGHT 2002 ACS
AB The reaction of H2NOH.HCl with MeNCO-K2CO3 gave 3-methyl-1-hydroxyurea, m.
126-8.degree., 1,5-dimethyl-3-hydroxybiuret, m. 119-21.degree., and N,N,O-tris(methylcarbamoyl)hydroxylamine, m. 155-8.degree.; the last is also obtained by treating H2NOH with excess of MeNCO. H2NOH in dioxane reacted with 0.01 and 0.02 mole PhCH2NCO to give 90% 3-benzyl-1-hydroxyurea m. 152-14.degree., and 1,5-dibenzyl-3-hydroxybiuret, m . 90-2.degree.. This reaction, carried out in dioxane and pyridine under reflux with 0.02 mole PhCH2NCO gave 93% N,N,O-tris(benzylcarbamoyl)hydroxylamine , m. 125-7.degree.. H2NOH gave with PhSO2NCO, MeC6H4SO2NCO, and PhCSNCS (under N) 92% 3-(benzenesulfonyl)-1-hydroxyurea m. 102-5.degree., 83% 1,5-bis(p-toluenesulfonyl)-3-hydroxybiuret, m. 125-7.degree., and 14% 3-(thiobenzoyl)-1-hydroxyurea, m.
173-5.degree.. The treatment of hydroxyurea H2O-KOH with BzCl gave N-carbamoyl-**O-benzoyl-hydroxylamine**, m.
126-8.degree.. H2NOH, treated with BzNCO, AcNCO, ClCH2CONCO, Cl2CHCONCO, and EtCONCO in dioxane gave 67% 3-benzoyl-1-hydroxyurea, m. 176-8.degree.,
95% 3-acetyl-1-hydroxyurea, m. 142-3.degree., 92% 3-(chloroacetyl)-1-hydroxyurea, m. 142.degree., 97% 3-(dichloroacetyl)-1-hydroxyurea, m. 135-7.degree., and 87% 3-propionyl-1-hydroxyurea, m. 148-50.degree.. MeONH2 reacted with BzNCO-Et2O in ClCH2CH2Cl-Et2O gave 97% 3-benzoyl 1-methoxyurea, m. 142-4.degree., and 94% 1,5-dibenzoyl-3-methoxybiuret, m.
127-9.degree.. MeNHOH and (MeNOH)2CH2 gave with BzNCO 62% 3-benzoyl-1-methyl-1-hydroxyurea, m. 134-6.degree. whereas MeNHOMe gave 95% 3-benzoyl-1-methyl-1-methoxyurea, m. 66-9.degree..
AN 72:54967 CA
TI Hydroxylamine derivatives. XXXVI. Carbamoylation of hydroxylamine
AU Zinner, Gerwalt; Stoffel, R.
CS Pharm. Chem., Tech. Univ. Braunschweig, Brunswick, Ger.
SO Arch. Pharm. (Weinheim, Ger.) (1969), 302(11), 838-47
CODEN: APBDAJ
DT Journal
LA German

L2 ANSWER 14 OF 14 CA COPYRIGHT 2002 ACS

AB Prepn. of I, where A is C2-5 alkylidene group and R is alkyl group, was described. Thus, 6.65 g. 97% benzoyl peroxide in 30 ml CHCl3 and 90 ml. anhyd. Et2O was added dropwise at 5.degree. in 45 min. to 13.2 g. 5-(3-methylaminopropylidene) - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene. After stirring at 0-5.degree. for 3 hrs., the pptd. 5-(3-methylaminopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene benzoate was sepd. and extd. with anhyd. Et2O. The filtrate was extd. with 2N Na2CO3, 2N HCl, and H2O, dried over Na2SO4 and evapd. to yield N-[3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)propyl]-N-methyl-O-benzoylhydroxylamine (II), m. 108-10.degree. (Et2O-n-C5H12). To 6.3 g. II in 150 ml. boiling EtOH were added 10 ml. H2O and 10 ml. 2N KOH. After cooling to 20.degree., the solvent was removed in vacuo, the residue dild. with 20 ml. H2O, extd. with Et2O, the ext. dried over Na2SO4, and concd. to yield N-[3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)propyl]-N-methylhydroxylamine (III), m. 93-4.degree. (Et2O-C5H12). Treatment of III in HCCl3 with an ethereal soln. of HCl gave III.HCl, m. 142-3.degree.. Similarly prepd. were

N-[3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-2-methylpropyl]-N-methyl-O-benzoylhydroxylamine, m. 78-80.degree.; 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-1-benzoyloxypyrrolidine, amorphous, Rf 0.85, thin-layer silica gel, C6H6-MeOH (3:1); 3-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ylidenemethyl)-1-benzoyloxypiperidine, amorphous, Rf 0.88 thin-layer silica gel, C6H6-MeOH (3:1); N-[3-(5H-dibenzo[a,d]cyclohepten-5-ylidene)propyl]-N-methyl-O-benzoylhydroxylamine, m. 137-8.degree.; N-[3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-2-methylpropyl]-N-methylhydroxylamine-HBr, m. 178-85.degree.; 3-(10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-ylidenemethyl)-1-hydroxypyrrolidine, amorphous, Rf 0.72, thin-layer silica gel, C6H6-MeOH (3:1); 2-[2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)ethyl]-1-hydroxypiperidine, m. 144-5.degree.; N-[3-(5H-dibenzo[a,d]cyclohepten-5-ylidene)propyl]-N-methylhydroxylamine, m. 99-100.degree.. According to a second method of prepn., 0.1 g. NaOMe in 20 ml. anhyd. MeOH was added to 3.7 g. N-[3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)propyl]-N-methyl-**O-benzoyl hydroxylamine**, suspended in 20 ml. anhyd. MeOH, the mixt. kept at 20.degree. for 2 hrs., refluxed for 5 min., and the solvent removed. Et2O and H2O were added to the residue. The Et2O layer was extd. with H2O and with HCl, the acid ext. treated with alkali, and extd. with Et2O to yield 2.1 g. III m. 93-4.degree..

AN 64:67613 CA

OREF 64:12621e-h,12622a

TI Tricyclic hydroxylamines as antidepressants

PA J. R. Geigy A.-G.

SO 10 pp.

DT Patent

LA Unavailable

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	NL 65005680		19651108	NL	
PRAI	CH		19640506		

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NEWS 3	Jan 29	FSTA has been reloaded and moves to weekly updates
NEWS 4	Feb 01	DKILIT now produced by FIZ Karlsruhe and has a new update frequency
NEWS 5	Feb 19	Access via Tymnet and SprintNet Eliminated Effective 3/31/02
NEWS 6	Mar 08	Gene Names now available in BIOSIS
NEWS 7	Mar 22	TOXLIT no longer available
NEWS 8	Mar 22	TRCTHERMO no longer available
NEWS 9	Mar 28	US Provisional Priorities searched with P in CA/CAplus and USPATFULL
NEWS 10	Mar 28	LIPINSKI/CALC added for property searching in REGISTRY
NEWS 11	Apr 02	PAPERCHEM no longer available on STN. Use PAPERCHEM2 instead.
NEWS 12	Apr 08	"Ask CAS" for self-help around the clock
NEWS 13	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 14	Apr 09	ZDB will be removed from STN
NEWS 15	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 16	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 17	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 18	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 19	Jun 03	New e-mail delivery for search results now available
NEWS 20	Jun 10	MEDLINE Reload
NEWS 21	Jun 10	PCTFULL has been reloaded

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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=> file ca, biosis, medline
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                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

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FILE 'BIOSIS' ENTERED AT 15:28:10 ON 18 JUN 2002
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FILE 'MEDLINE' ENTERED AT 15:28:10 ON 18 JUN 2002

=> s alanyl-pyrolidide? or isoleucyl-thiazolidide? or n-valyl-prolyl? or
(o-benzoyl hydroxylamine?) or aminoacyl-thiazolidide?
L1          15 ALANYL-PYROLIDIDE? OR ISOLEUCYL-THIAZOLIDIDE? OR
N-VALYL-PROLYL?
               OR (O-BENZOYL HYDROXYLAMINE?) OR AMINOACYL-THIAZOLIDIDE?

=> dup rem l1
PROCESSING COMPLETED FOR L1
L2           14 DUP REM L1 (1 DUPLICATE REMOVED)

=> d 1-14 ab,bib

L2   ANSWER 1 OF 14     MEDLINE
AB   In the CBA x DBA/2 mouse model, stress-triggered abortions are mediated
by
     a Th1-like cytokine response of decidual lymphocytes. The factors that
     determine the cytokine pattern leading to abortion are currently unknown.
     Dipeptidyl Peptidase IV (DP IV) enhances Th1-cytokine responses and
     impairs the evolvement of a Th2 cytokine profile. The T-cell-activation
     antigen, CD26, possesses DP IV activity. The aim of the present study was
     to investigate the role of DP IV activity and CD26-positive decidual
     lymphocytes in murine stress-triggered abortions by inhibition of DP IV
     activity. DBA/2-mated CBA mice were stressed on day 5.5 of pregnancy and
     received daily injections of an inhibitor of DP IV activity,
     Ile-thiazolidide (20 micromol/kg). On day 13 of gestation, the animals
     were sacrificed and the percentage of implants and abortions documented.
     CD26-positive lymphocytes in spleen and uterine decidua and the
     intracellular cytokines interferon (IFN)-gamma and interleukin (IL)-10
     were determined by flow cytometry. Stressed and nonstressed animals
     receiving an inactive stereoisomeric form were used as controls. In mice
     receiving the DP IV inhibitor, stress failed to boost the abortion rate
     (37.2% versus 13.6%, P < 0.01). IFN-gamma producing cells were increased
     in stressed animals, but returned to the baseline upon the inhibition of
     DP IV. The number of IL-10 producing cells was reduced in stressed
     animals, independent from DP IV inhibition.
AN   2001249247     MEDLINE
DN   21206358   PubMed ID: 11309152
TI   Inhibition of dipeptidyl peptidase IV (DP IV, CD26) activity abrogates
     stress-induced, cytokine-mediated murine abortions.
AU   Hildebrandt M; Arck P C; Kruber S; Demuth H U; Reutter W; Klapp B F
CS   Medizinische Klinik m.S. Psychosomatik, Charite, Humboldt-Universitat zu
```

Berlin, Germany.. hildebra@charite.de
SO SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (2001 May) 53 (5) 449-54.
Journal code: 0323767. ISSN: 0300-9475.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200105
ED Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010510

L2 ANSWER 2 OF 14 MEDLINE
AB Glucagon is a 29-amino acid polypeptide released from pancreatic islet alpha-cells that acts to maintain euglycemia by stimulating hepatic glycogenolysis and gluconeogenesis. Despite its importance, there remains controversy about the mechanisms responsible for glucagon clearance in the body. In the current study, enzymatic metabolism of glucagon was assessed using sensitive mass spectrometric techniques to identify the molecular products. Incubation of glucagon with purified porcine dipeptidyl peptidase IV (DP IV) yielded sequential production of glucagon(3-29) and glucagon(5-29). In human serum, degradation to glucagon(3-29) was rapidly followed by N-terminal cyclization of glucagon, preventing further DP IV-mediated hydrolysis. Bioassay of glucagon, following incubation with purified DP IV or normal rat serum demonstrated a significant loss of hyperglycemic activity, while a similar incubation in DP IV-deficient rat serum did not show any loss of glucagon bioactivity. Degradation, monitored by mass spectrometry and bioassay, was blocked by the specific DP IV inhibitor, isoleucyl thiazolidine. These results identify DP IV as a primary enzyme involved in the degradation and inactivation of glucagon. These findings have important implications for the determination of glucagon levels in human plasma.
AN 2001136578 MEDLINE
DN 20564737 PubMed ID: 11111019
TI Metabolism of glucagon by dipeptidyl peptidase IV (CD26).
AU Pospisilik J A; Hinke S A; Pederson R A; Hoffmann T; Rosche F; Schlenzig D; Glund K; Heiser U; McIntosh C H; Demuth H
CS Department of Physiology, University of British Columbia, British Columbia, V6T 1Z3, Vancouver, Canada.
SO REGULATORY PEPTIDES, (2001 Jan 12) 96 (3) 133-41.
Journal code: 8100479. ISSN: 0167-0115.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200103
ED Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010301

L2 ANSWER 3 OF 14 CA COPYRIGHT 2002 ACS
AB A method is provided with which, by inhibiting dipeptidyl peptidase IV (DPIV) and/or DPIV-analogous enzyme activity in the blood of a mammal, the endogenous (or addnl. exogenously administered) glycogenolytic peptide glucagon (or analogs thereof) degraded by DPIV and DPIV-analogous enzymes is reduced, and thus the decrease in concn. of this peptide hormone and/or

its analogs is retarded. Through the effect obtained with the DPIV inhibitors, there is increased stability of the (endogenous or exogenous) glucagon/glucagon analogs, thereby increasing glycogenolytic stimulation of glucagon receptors, in particular in liver cells, changing the duration of effectiveness of the body's glucagon, involving a stimulation of the carbohydrate metab. As result, the blood sugar level rises over the glucose concn. characteristic of hypoglycemia in the serum of the treated organism. Thus, metabolic anomalies, e.g. hypoglycemic conditions, which are the result of decreased glucose concns. in the blood., are prevented and/or ameliorated. The method of the invention represents a new approach for increasing endogenous blood glucose concn. It is simple, and com. useful. The effect of DPIV inhibitor **isoleucyl thiazolidide** is presented.

AN 132:117551 CA
TI Procedure for the increase of the blood glucose level in mammals
IN Demuth, Hans-Ulrich; Hoffmann, Torsten; Kuhn-Wache, Kerstin; Rosche, Fred
PA Probiodrug Gesellschaft fur Arzneimittelforschung m.b.H., Germany
SO Ger. Offen., 8 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19834591	A1	20000203	DE 1998-19834591	19980731
	EP 995440	A1	20000426	EP 1999-115236	19990802
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	US 6319893	B1	20011120	US 1999-365404	19990802
	US 2002071838	A1	20020613	US 2001-682968	20011102
PRAI	DE 1998-19834591	A	19980731		
	US 1999-365404	A3	19990802		

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 14 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:239685 BIOSIS
DN PREV200100239685
TI DP IV-inhibitors: Potential antidiabetic drugs.
AU Schlenzig, D. (1); Kruber, S. (1); White, H. A.; Pederson, R. A.; Demuth, H.-U. (1)
CS (1) Probiodrug Gesellschaft fuer Arzneimittelforschung mbH, Weinbergweg 22, 06120, Halle Germany
SO Fields, Gregg B.; Tam, James P.; Barany, George. (2000) pp. 224-226. Peptides for the new millennium. print.
Publisher: Kluwer Academic Publishers 3300 AA, Dordrecht, Netherlands.
Meeting Info.: 16th American Peptide Symposium Minneapolis, MI, USA June 26-July 01, 1999
ISBN: 0-7923-6445-7 (cloth).
DT Book; Conference
LA English
SL English

L2 ANSWER 5 OF 14 MEDLINE
AB Dipeptidyl peptidase IV is known to be involved, due to both hydrolytic and non-hydrolytic mechanisms, in various cell functions of normal and cancer cells as well. In this report dipeptidyl peptidase IV substrate and

pH preferences, some inhibition parameters, freezing/thawing sensitivity and stability against hydrolysis by trypsin were studied in C6 rat glioma cells. Our results confirmed substantial heterogeneity of dipeptidyl peptidase IV population. Such observation is important to avoid methodological artifacts and to decrease risk of misinterpretations in biological studies.

AN 2000439421 MEDLINE
DN 20439658 PubMed ID: 10985474
TI Heterogeneity of dipeptidyl peptidase IV from C6 rat glioma cells.
AU Malik R; Vlasicova L; Kadlecova L; Sedo A
CS 1st Department of Medical Chemistry and Biochemistry, 1st Faculty of Medicine, Charles University, Prague 2, Czech Republic.
SO NEOPLASMA, (2000) 47 (2) 96-9.
Journal code: 0377266. ISSN: 0028-2685.
CY Slovakia
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200009
ED Entered STN: 20000928
Last Updated on STN: 20000928
Entered Medline: 20000915

L2 ANSWER 6 OF 14 MEDLINE
AN 1999424399 MEDLINE
DN 99424399 PubMed ID: 10494612
TI [Inhibition of incretin degradation--a new therapy principle for treatment
of type 2 diabetes?].
Inhibition der Inkretindegradation--ein neues Therapieprinzip zur Behandlung des Typ-2-Diabetes?.
AU Gallwitz B; Schmidt W E
CS Medizinische Klinik I, St.-Josef-Hospital, Ruhr-Universitat Bochum.
SO ZEITSCHRIFT FUR GASTROENTEROLOGIE, (1999 Aug) 37 (8) 755-60.
Journal code: 0033370. ISSN: 0044-2771.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA German
FS Priority Journals
EM 199911
ED Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991119

L2 ANSWER 7 OF 14 MEDLINE
AB The incretins glucose-dependent insulinotropic polypeptide (GIP1-42) and truncated forms of glucagon-like peptide-1 (GLP-1) are hormones released from the gut in response to ingested nutrients, which act on the pancreas to potentiate glucose-induced insulin secretion. These hormones are rapidly inactivated by the circulating enzyme dipeptidyl peptidase IV ([DPIV] CD26). This study describes the effect on glucose tolerance and insulin secretion of inhibiting endogenous DPIV in the rat using Ile-thiazolidide, a specific DPIV inhibitor. High-performance liquid chromatography (HPLC) analysis of plasma following in vivo administration of 125I-labeled peptides showed that inhibition of DPIV by about 70% prevented the degradation of 90.0% of injected 125I-GLP-17-36 after 5 minutes, while only 13.4% remained unhydrolyzed in rats not treated with the DPIV-inhibiting agent after only 2 minutes. Ile-thiazolidide treatment
also increased the circulating half-life of intact GLP-17-36 released in

response to intraduodenal (ID) glucose (as measured by N-terminal specific radioimmunoassay [RIA]). In addition, inhibition of DPIV in vivo resulted in an earlier increase and peak of plasma insulin and a more rapid clearance of blood glucose in response to ID glucose challenge. When considered with the HPLC data, these results suggest that the altered insulin profile is an incretin-mediated response. DPIV inhibition resulting in improved glucose tolerance may have therapeutic potential for the management of type 2 diabetes mellitus.

AN 1999191906 MEDLINE
DN 99191906 PubMed ID: 10094118
TI Improved glucose tolerance in rats treated with the dipeptidyl peptidase IV (CD26) inhibitor Ile-thiazolidide.
AU Pauly R P; Demuth H U; Rosche F; Schmidt J; White H A; Lynn F; McIntosh C H; Pederson R A
CS Department of Physiology, University of British Columbia, Vancouver, Canada.
SO METABOLISM: CLINICAL AND EXPERIMENTAL, (1999 Mar) 48 (3) 385-9. Journal code: 0375267. ISSN: 0026-0495.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199904
ED Entered STN: 19990426
Last Updated on STN: 19990426
Entered Medline: 19990413

L2 ANSWER 8 OF 14 CA COPYRIGHT 2002 ACS DUPLICATE 1
AB The conjugate addn. of N-BOC-**O-benzoyl hydroxylamine** catalyzed by NaH to chiral .alpha.,.beta.-unsatd. imide I gives protected benzoyloxyaminopropanoyl deriv. II. II undergoes cyclization on treatment with sodium or lithium bases to give aziridine-2-imide III in good yield and diastereoselectivity. When N-BOC-**O-benzoyl hydroxylamine** is deprotonated with stoichiometric lithium or sodium bases, the intermediate enolate resulting from 1,4-addn. to I spontaneously undergoes cyclization affording in a single step the N-BOC aziridine III in higher yield.
AN 129:175937 CA
TI Diastereoselective synthesis of 3'-unsubstituted N-Boc-aziridine from a readily available chiral .alpha.,.beta.-unsaturated imide
AU Cardillo, Giuliana; Gentilucci, Luca; Bastardas, Imma Ratera; Tolomelli, Alessandra
CS Dip. Chim. "G. Ciamician" and CSFM-CNR, Univ. Bologna, Bologna, 40126, Italy
SO Tetrahedron (1998), 54(28), 8217-8222
CODEN: TETRAB; ISSN: 0040-4020
PB Elsevier Science Ltd.
DT Journal
LA English
OS CASREACT 129:175937

L2 ANSWER 9 OF 14 MEDLINE
AB The hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP)-1 act on the pancreas to potentiate glucose-induced insulin secretion (enteroinsular axis). These hormones (incretins) are rapidly hydrolyzed by the circulating enzyme dipeptidyl

peptidase IV (DP IV) into biologically inactive NH2-terminally truncated fragments. This study describes the effect of inhibiting endogenous DP IV with a specific DP IV inhibitor, isoleucine thiazolidide (Ile-thiazolidide), on glucose tolerance and insulin secretion in the obese Zucker rat. In initial studies, the specificity of Ile-thiazolidide as an inhibitor of incretin degradation was determined using matrix-assisted laser desorption/ionization-time of flight mass spectrometry. These results showed that inhibiting DP IV activity with Ile-thiazolidide blocked the formation of NH2-terminally truncated GIP and GLP-1. Oral administration of Ile-thiazolidide resulted in rapid inhibition of circulating DP IV levels by 65% in obese and lean Zucker rats. Suppression of DP IV levels enhanced insulin secretion in both phenotypes with the most dramatic effect occurring in obese animals (150% increase in integrated insulin response vs. 27% increase in lean animals).

Ile-thiazolidide treatment improved glucose tolerance in both phenotypes and restored glucose tolerance to near-normal levels in obese animals. This was attributed to the glucose-lowering actions of increasing the circulating half-lives of the endogenously released incretins GIP and, particularly, GLP-1. This study suggests that drug manipulation of plasma incretin activity by inhibiting the enzyme DP IV is a valid therapeutic approach for lowering glucose levels in NIDDM and other disorders involving glucose intolerance.

AN 1998366885 MEDLINE
DN 98366885 PubMed ID: 9703325
TI Improved glucose tolerance in Zucker fatty rats by oral administration of the dipeptidyl peptidase IV inhibitor isoleucine thiazolidide.
AU Pederson R A; White H A; Schlenzig D; Pauly R P; McIntosh C H; Demuth H U
CS Department of Physiology, University of British Columbia, Vancouver, Canada.. pederson@unixg.ubc.ca
SO DIABETES, (1998 Aug) 47 (8) 1253-8.
Journal code: 0372763. ISSN: 0012-1797.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199809
ED Entered STN: 19980917
Last Updated on STN: 20000303
Entered Medline: 19980909

L2 ANSWER 10 OF 14 CA COPYRIGHT 2002 ACS
AB Administration of agents which lower the blood dipeptidyl peptidase IV activity decreases the degrdn. of the (endogenous or exogenous) insulinotropic peptides, (1-42)-gastric inhibitory polypeptide and (7-36)-glucagonlike peptide 1 amide, and consequently enhances the insulinotropic stimulation of integrin receptors on pancreatic islet cells, stimulates carbohydrate metab., and decreases the serum glucose level. Thus, **isoleucyl thiazolidide** (0.1 mg i.v.) administration to rats after intraduodenal administration of glucose dose-dependently lowered the blood glucose level.
AN 127:341803 CA
TI Method for lowering the blood glucose level in mammals
IN Demuth, Hans-Ulrich; Rosche, Fred; Schmidt, Joern; Pauly, Robert P.; Mclntosh, Christopher H. S.; Pederson, Ray A.
PA Hans-Knoell-Institut fuer Naturstoff-Forschung e.V., Germany
SO Ger. Offen., 7 pp.
CODEN: GWXXBX
DT Patent

LA German
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19616486	A1	19971030	DE 1996-19616486	19960425
	DE 19616486	C2	19990812		
	CA 2252576	AA	19971106	CA 1997-2252576	19970424
	WO 9740832	A1	19971106	WO 1997-DE820	19970424
	W: AU, CA, CN, JP, KR, MX, NZ, RU, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9730233	A1	19971119	AU 1997-30233	19970424
	AU 721477	B2	20000706		
	EP 896538	A1	19990217	EP 1997-924866	19970424
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	CN 1216468	A	19990512	CN 1997-194017	19970424
	EP 1084705	A2	20010321	EP 2000-119496	19970424
	EP 1084705	A3	20020515		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	AT 202705	E	20010715	AT 1997-924866	19970424
	JP 2001510442	T2	20010731	JP 1997-538453	19970424
	ES 2158562	T3	20010901	ES 1997-924866	19970424
	US 6303661	B1	20011016	US 1998-155833	19981006
PRAI	DE 1996-19616486	A	19960425		
	EP 1997-924866	A3	19970424		
	WO 1997-DE820	W	19970424		

L2 ANSWER 11 OF 14 CA COPYRIGHT 2002 ACS
AB The mechanism of inactivation of serine proteases by N-peptidyl-O-aroylhydroxylamines was studied by X-ray crystallog. Cocrystals of subtilisin Carlsberg inactivated with N-((tert-butoxycarbonyl)alanylprolylphenylalanyl)-O-nitrobenzoyl hydroxylamine were grown, and diffraction data to 1.8-.ANG. resoln. were obtained. The resulting electron d. maps clearly reveal that the .gamma.-oxygen of the catalytic serine forms a carbamate deriv. with the inhibitor. The peptide part of the inhibitor does not form the usual antiparallel .beta.-sheet in the P binding cleft but protrudes out of the active site and is stabilized by a network of water mols. These results, combined with kinetic characterization reported previously [Demuth, H.-U., Schoenlein, C., & Barth, A.(1989b) Biochim. Biophys. Acta 996, 19-22; Schmidt, C., Schmidt, R., & Demuth, H.-U. (1990) Peptides (Giralt, E., & Andreu, D., Eds.) ESCOM Science Publishers B.V., New York] support the existence of at least one intermediate between the formation of the Michaelis complex and the final product. The authors suggest a mechanism for the inactivation of subtilisin Carlsberg by N-((tert-butoxycarbonyl)alanylprolylphenylalanyl)-**O-benzoyl hydroxylamine** whereby a neg. charged Michaelis complex undergoes a Lossen rearrangement giving rise to an isocyanate intermediate that reacts with the side chain of the active site serine.
AN 121:128521 CA
TI Inactivation of Subtilisin Carlsberg by N-((tert-

Butoxycarbonyl)alanylprolylphenylalanyl)-**O-benzoyl Hydroxylamine**: Formation of a Covalent Enzyme-Inhibitor Linkage in the Form of a Carbamate Derivative
AU Steinmetz, Anke C. U.; Demuth, Hans-Ulrich; Ringe, Dagmar
CS Department of Biochemistry and Chemistry, Brandeis University, Waltham, MA, 02254, USA
SO Biochemistry (1994), 33(34), 10535-44
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English

L2 ANSWER 12 OF 14 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1975:201028 BIOSIS
DN BA60:31024
TI MECHANISM OF CYTOCHROME C PEROXIDASE EC-1.11.1.5 **O BENZOYL HYDROXYLAMINE** AS AN ANALOG OF HYDROGEN PER OXIDE.
AU COULSON A F W; YONETANI T
SO BIOCHEMISTRY, (1975) 14 (11), 2389-2396.
CODEN: BICHAW. ISSN: 0006-2960.
FS BA; OLD
LA Unavailable

L2 ANSWER 13 OF 14 CA COPYRIGHT 2002 ACS
AB The reaction of H2NOH.HCl with MeNCO-K2CO3 gave 3-methyl-1-hydroxyurea, m.
126-8.degree., 1,5-dimethyl-3-hydroxybiuret, m. 119-21.degree., and N,N,O-tris(methylcarbamoyl)hydroxylamine, m. 155-8.degree.; the last is also obtained by treating H2NOH with excess of MeNCO. H2NOH in dioxane reacted with 0.01 and 0.02 mole PhCH2NCO to give 90% 3-benzyl-1-hydroxyurea m. 152-14.degree., and 1,5-dibenzyl-3-hydroxybiuret, m . 90-2.degree.. This reaction, carried out in dioxane and pyridine under reflux with 0.02 mole PhCH2NCO gave 93% N,N,O-tris(benzylcarbamoyl)hydroxylamine , m. 125-7.degree.. H2NOH gave with PhSO2NCO, MeC6H4SO2NCO, and PhCSNCS (under N) 92% 3-(benzenesulfonyl)-1-hydroxyurea m. 102-5.degree., 83% 1,5-bis(p-toluenesulfonyl)-3-hydroxybiuret, m. 125-7.degree., and 14% 3-(thiobenzoyl)-1-hydroxyurea, m.
173-5.degree.. The treatment of hydroxyurea H2O-KOH with BzCl gave N-carbamoyl-**O-benzoyl-hydroxylamine**, m.
126-8.degree.. H2NOH, treated with BzNCO, AcNCO, ClCH2CONCO, Cl2CHCONCO, and EtCONCO in dioxane gave 67% 3-benzoyl-1-hydroxyurea, m. 176-8.degree.,
95% 3-acetyl-1-hydroxyurea, m. 142-3.degree., 92% 3-(chloroacetyl)-1-hydroxyurea, m. 142.degree., 97% 3-(dichloroacetyl)-1-hydroxyurea, m. 135-7.degree., and 87% 3-propionyl-1-hydroxyurea, m. 148-50.degree.. MeONH2 reacted with BzNCO-Et2O in ClCH2CH2Cl-Et2O gave 97% 3-benzoyl 1-methoxyurea, m. 142-4.degree., and 94% 1,5-dibenzoyl-3-methoxybiuret, m.
127-9.degree.. MeNHOH and (MeNOH)2CH2 gave with BzNCO 62% 3-benzoyl-1-methyl-1-hydroxyurea, m. 134-6.degree. whereas MeNHOMe gave 95% 3-benzoyl-1-methyl-1-methoxyurea, m. 66-9.degree..
AN 72:54967 CA
TI Hydroxylamine derivatives. XXXVI. Carbamoylation of hydroxylamine
AU Zinner, Gerwalt; Stoffel, R.
CS Pharm. Chem., Tech. Univ. Braunschweig, Brunswick, Ger.
SO Arch. Pharm. (Weinheim, Ger.) (1969), 302(11), 838-47
CODEN: APBDAJ
DT Journal
LA German

L2 ANSWER 14 OF 14 CA COPYRIGHT 2002 ACS

AB Prepn. of I, where A is C2-5 alkylidene group and R is alkyl group, was described. Thus, 6.65 g. 97% benzoyl peroxide in 30 ml CHCl3 and 90 ml. anhyd. Et2O was added dropwise at 5.degree. in 45 min. to 13.2 g. 5-(3-methylaminopropylidene) - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene. After stirring at 0-5.degree. for 3 hrs., the pptd. 5-(3-methylaminopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene benzoate was sepd. and extd. with anhyd. Et2O. The filtrate was extd. with 2N Na2CO3, 2N HCl, and H2O, dried over Na2SO4 and evapd. to yield N-[3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)propyl]-N-methyl-O-benzoylhydroxylamine (II), m. 108-10.degree. (Et2O-n-C5H12). To 6.3 g. II in 150 ml. boiling EtOH were added 10 ml. H2O and 10 ml. 2N KOH. After cooling to 20.degree., the solvent was removed in vacuo, the residue dild. with 20 ml. H2O, extd. with Et2O, the ext. dried over Na2SO4, and concd. to yield N-[3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)propyl]-N-methylhydroxylamine (III), m. 93-4.degree. (Et2O-C5H12). Treatment of III in HCCl3 with an ethereal soln. of HCl gave III.HCl, m. 142-3.degree.. Similarly prepd. were

N-[3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-2-methylpropyl]-N-methyl-O-benzoylhydroxylamine, m. 78-80.degree.; 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidenemethyl)-1-benzoyloxypyrrolidine, amorphous, Rf 0.85, thin-layer silica gel, C6H6-MeOH (3:1); 3-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-ylidenemethyl)-1-benzoyloxypiperidine, amorphous, Rf 0.88 thin-layer silica gel, C6H6-MeOH (3:1); N-[3-(5H-dibenzo[a,d]cyclohepten-5-ylidene)propyl]-N-methyl-O-benzoylhydroxylamine, m. 137-8.degree.; N-[3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-2-methylpropyl]-N-methylhydroxylamine-HBr, m. 178-85.degree.; 3-(10,11-dihydro-5H-dibenzo-[a,d]cyclohepten-5-ylidenemethyl)-1-hydroxypyrrolidine, amorphous, Rf 0.72, thin-layer silica gel, C6H6-MeOH (3:1); 2-[2-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)ethyl]-1-hydroxypiperidine, m. 144-5.degree.; N-[3-(5H-dibenzo[a,d]cyclohepten-5-ylidene)propyl]-N-methylhydroxylamine, m. 99-100.degree.. According to a second method of prepn., 0.1 g. NaOMe in 20 ml. anhyd. MeOH was added to 3.7 g. N-[3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)propyl]-N-methyl-**O-benzoyl hydroxylamine**, suspended in 20 ml. anhyd. MeOH, the mixt. kept at 20.degree. for 2 hrs., refluxed for 5 min., and the solvent removed. Et2O and H2O were added to the residue. The Et2O layer was extd. with H2O and with HCl, the acid ext. treated with alkali, and extd. with Et2O to yield 2.1 g. III m. 93-4.degree..

AN 64:67613 CA

OREF 64:12621e-h,12622a

TI Tricyclic hydroxylamines as antidepressants

PA J. R. Geigy A.-G.

SO 10 pp.

DT Patent

LA Unavailable

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	NL 65005680		19651108	NL	
PRAI	CH		19640506		

=> s (dp iv inhibitor?) or (dipeptidyl peptidase iv inhibitor?)

L3 184 (DP IV INHIBITOR?) OR (DIPEPTIDYL PEPTIDASE IV INHIBITOR?)

```
=> s blood sugar?
L4       41519 BLOOD SUGAR?

=> s increas? or rais? or ris?
L5     7843900 INCREAS? OR RAIS? OR RIS?

=> s l3 and l4 and l5
L6           2 L3 AND L4 AND L5

=> d 1-2 ab,bib

L6   ANSWER 1 OF 2  CA  COPYRIGHT 2002 ACS
AB   A method is provided with which, by inhibiting dipeptidyl peptidase IV
     (DPIV) and/or DPIV-analogous enzyme activity in the blood of a mammal,
the
     endogenous (or addnl. exogenously administered) glycogenolytic peptide
     glucagon (or analogs thereof) degraded by DPIV and DPIV-analogous enzymes
     is reduced, and thus the decrease in concn. of this peptide hormone
and/or
     its analogs is retarded.  Through the effect obtained with the DPIV
     inhibitors, there is increased stability of the (endogenous or
     exogenous) glucagon/glucagon analogs, thereby increasing
     glycogenolytic stimulation of glucagon receptors, in particular in liver
     cells, changing the duration of effectiveness of the body's glucagon,
     involving a stimulation of the carbohydrate metab.  As result, the
     blood sugar level rises over the glucose
     concn. characteristic of hypoglycemia in the serum of the treated
     organism.  Thus, metabolic anomalies, e.g. hypoglycemic conditions, which
     are the result of decreased glucose concns. in the blood., are prevented
     and/or ameliorated.  The method of the invention represents a new
approach
     for increasing endogenous blood glucose concn.  It is simple,
     and com. useful.  The effect of DPIV inhibitor isoleucyl thiazolidide is
     presented.
AN   132:117551  CA
TI   Procedure for the increase of the blood glucose level in mammals
IN   Demuth, Hans-Ulrich; Hoffmann, Torsten; Kuhn-Wache, Kerstin; Rosche, Fred
PA   Probiodrug Gesellschaft fur Arzneimittelforschung m.b.H., Germany
SO   Ger. Offen., 8 pp.
     CODEN: GWXXBX
DT   Patent
LA   German
FAN.CNT 1
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
PI   DE 19834591        A1   20000203       DE 1998-19834591 19980731
     EP 995440          A1   20000426       EP 1999-115236   19990802
          R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
              IE, SI, LT, LV, FI, RO
     US 6319893         B1   20011120       US 1999-365404   19990802
     US 2002071838      A1   20020613       US 2001-682968   20011102
PRAI DE 1998-19834591  A    19980731
     US 1999-365404    A3   19990802
RE.CNT  4      THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6   ANSWER 2 OF 2  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AB   A method of raising the blood sugar level in
     a mammal having hypoglycemia is described. The method reduces degradation
     of glucagon by administering to the mammal a therapeutically effective
```

amount of an inhibitor of dipeptidyl peptidase IV and physiologically acceptable adjuvants and/or excipients.
AN 2002:71768 BIOSIS
DN PREV200200071768
TI **Raising blood sugar** level in hypoglycemic mammals by administering inhibitors of dipeptidyl peptidase IV.
AU Demuth, Hans-Ulrich (1); Hoffmann, Torsten; Kuhn-Wache, Kerstin; Rosche, Fred
CS (1) Halle/Saale Germany
ASSIGNEE: Probiodrug, Halle, Germany
PI US 6319893 November 20, 2001
SO Official Gazette of the United States Patent and Trademark Office Patents,
(Nov. 20, 2001) Vol. 1252, No. 3, pp. No Pagination.
ftp://ftp.uspto.gov/pub/patdata/. e-file.
ISSN: 0098-1133.
DT Patent
LA English

=> d his

(FILE 'HOME' ENTERED AT 15:27:52 ON 18 JUN 2002)

FILE 'CA, BIOSIS, MEDLINE' ENTERED AT 15:28:10 ON 18 JUN 2002
L1 15 S ALANYL-PYROLIDIDE? OR ISOLEUCYL-THIAZOLIDIDE? OR N-VALYL-PROL
L2 14 DUP REM L1 (1 DUPLICATE REMOVED)
L3 184 S (DP IV INHIBITOR?) OR (DIPEPTIDYL PEPTIDASE IV INHIBITOR?)
L4 41519 S BLOOD SUGAR?
L5 7843900 S INCREAS? OR RAIS? OR RIS?
L6 2 S L3 AND L4 AND L5

=> s hypoglycaemia?
L7 5962 HYPOGLYCAEMIA?

=> s l3 or l1 and l7
L8 184 L3 OR L1 AND L7

=> s l7 (p) (l3 or l1)
L9 0 L7 (P) (L3 OR L1)

=> s l7 and (l3 or l1)
L10 0 L7 AND (L3 OR L1)

=> dipeptidyl peptidase?
DIPEPTIDYL IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s dipeptidyl peptidase?
L11 4447 DIPEPTIDYL PEPTIDASE?

=> s l11 and l7
L12 1 L11 AND L7

=> d

L12 ANSWER 1 OF 1 MEDLINE

AN 1999451234 MEDLINE
DN 99451234 PubMed ID: 10519910
TI Glucagon-like peptide-1, a gastrointestinal hormone with a pharmaceutical potential.
AU Holst J J
CS Department of Medical Physiology, University of Copenhagen, the Panum institute, Blegdamsvej 3, Copenhagen N, DK-2200, Denmark.
SO CURRENT MEDICINAL CHEMISTRY, (1999 Nov) 6 (11) 1005-17. Ref: 125
Journal code: 9440157. ISSN: 0929-8673.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199912
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991215

=> d ab,bib

L12 ANSWER 1 OF 1 MEDLINE
AB Glucagon-like peptide-1 (GLP-1) is an insulinotropic hormone secreted from endocrine cells in the gut mucosa in response to meal ingestion. It is an important incretin hormone; mice with a null mutation in the GLP-1 receptor gene develop glucose intolerance. In addition, it inhibits gastrointestinal secretion and motility and is thought to be part of the "ileal brake" mechanism. Perhaps because of the latter actions it inhibits food intake, but intracerebral injection of GLP-1 also inhibits food intake. The insulinotropic effect is preserved in patients with type 2 diabetes mellitus, in whom also glucagon secretion is inhibited. Thus upon i.v. GLP-1 infusion blood glucose may be completely normalised. Because its actions are glucose-dependent **hypoglycaemia** does not develop. However, GLP-1 is metabolised extremely rapidly in vivo, initially by a mechanism that involves the enzyme **dipeptidyl peptidase**-IV. It is currently being investigated how GLP-1 or analogues thereof can be employed in practical diabetes therapy. Promising solutions include the development of stable analogues and inhibitors of the degrading enzyme.
AN 1999451234 MEDLINE
DN 99451234 PubMed ID: 10519910
TI Glucagon-like peptide-1, a gastrointestinal hormone with a pharmaceutical potential.
AU Holst J J
CS Department of Medical Physiology, University of Copenhagen, the Panum institute, Blegdamsvej 3, Copenhagen N, DK-2200, Denmark.
SO CURRENT MEDICINAL CHEMISTRY, (1999 Nov) 6 (11) 1005-17. Ref: 125
Journal code: 9440157. ISSN: 0929-8673.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals

EM 199912
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991215

=> s hyperglycemi?
L13 52377 HYPERGLYCEMI?

=> d his

(FILE 'HOME' ENTERED AT 15:27:52 ON 18 JUN 2002)

FILE 'CA, BIOSIS, MEDLINE' ENTERED AT 15:28:10 ON 18 JUN 2002
L1 15 S ALANYL-PYROLIDIDE? OR ISOLEUCYL-THIAZOLIDIDE? OR N-VALYL-PROL
L2 14 DUP REM L1 (1 DUPLICATE REMOVED)
L3 184 S (DP IV INHIBITOR?) OR (DIPEPTIDYL PEPTIDASE IV INHIBITOR?)
L4 41519 S BLOOD SUGAR?
L5 7843900 S INCREAS? OR RAIS? OR RIS?
L6 2 S L3 AND L4 AND L5
L7 5962 S HYPOGLYCAEMIA?
L8 184 S L3 OR L1 AND L7
L9 0 S L7 (P) (L3 OR L1)
L10 0 S L7 AND (L3 OR L1)
L11 4447 S DIPEPTIDYL PEPTIDASE?
L12 1 S L11 AND L7
L13 52377 S HYPERGLYCEMI?

=> s l13 and (l1 or l3)
L14 5 L13 AND (L1 OR L3)

=> dup rem l14
PROCESSING COMPLETED FOR L14
L15 3 DUP REM L14 (2 DUPLICATES REMOVED)

=> d 1-3 ab,bib

L15 ANSWER 1 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:576050 BIOSIS
DN PREV200100576050
TI P32/98. Antidiabetic, **dipeptidyl-peptidase IV inhibitor**.
AU Sorbera, L. A. (1); Revel, L. (1); Castaner, J. (1)
CS (1) Prous Science, 08080, Barcelona Spain
SO Drugs of the Future, (September, 2001) Vol. 26, No. 9, pp. 859-864. print.
ISSN: 0377-8282.
DT Article
LA English
SL English

L15 ANSWER 2 OF 3 CA COPYRIGHT 2002 ACS DUPLICATE 1
AB Glucagon is a 29-amino acid polypeptide released from pancreatic islet .alpha.-cells that acts to maintain euglycemia by stimulating hepatic glycogenolysis and gluconeogenesis. Despite its importance, there remains controversy about the mechanisms responsible for glucagon clearance in the body. In the current study, enzymic metab. of glucagon was assessed using

sensitive mass spectrometric techniques to identify the mol. products. Incubation of glucagon with purified porcine dipeptidyl peptidase IV (DP IV) yielded sequential prodn. of glucagon3-29 and glucagon5-29. In human serum, degrdn. to glucagon3-29 was rapidly followed by N-terminal cyclization of glucagon, preventing further DP IV-mediated hydrolysis. Bioassay of glucagon, following incubation with purified DP IV or normal rat serum demonstrated a significant loss of **hyperglycemic** activity, while a similar incubation in DP IV-deficient rat serum did not show any loss of glucagon bioactivity. Degrdn., monitored by mass spectrometry and bioassay, was blocked by the specific **DP IV inhibitor**, isoleucyl thiazolidine. These results identify DP IV as a primary enzyme involved in the degrdn. and inactivation of glucagon. These findings have important implications for the detn. of glucagon levels in human plasma.

AN 134:95720 CA
TI Metabolism of glucagon by dipeptidyl peptidase IV (CD26)
AU Pospisilik, J. A.; Hinke, S. A.; Pederson, R. A.; Hoffmann, T.; Rosche, F.; Schlenzig, D.; Glund, K.; Heiser, U.; McIntosh, C. H. S.; Demuth, H.-U.
CS Department of Physiology, University of British Columbia, Vancouver, BC, V6T 1Z3, Can.
SO Regulatory Peptides (2001), 96(3), 133-141
CODEN: REPPDY; ISSN: 0167-0115
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 3 OF 3 CA COPYRIGHT 2002 ACS
AB A method is provided with which, by inhibiting dipeptidyl peptidase IV (DPIV) and/or DPIV-analogous enzyme activity in the blood of a mammal, the endogenous (or addnl. exogenously administered) glycogenolytic peptide glucagon (or analogs thereof) degraded by DPIV and DPIV-analogous enzymes is reduced, and thus the decrease in concn. of this peptide hormone and/or its analogs is retarded. Through the effect obtained with the DPIV inhibitors, there is increased stability of the (endogenous or exogenous) glucagon/glucagon analogs, thereby increasing glycogenolytic stimulation of glucagon receptors, in particular in liver cells, changing the duration of effectiveness of the body's glucagon, involving a stimulation of the carbohydrate metab. As result, the blood sugar level rises over the glucose concn. characteristic of hypoglycemia in the serum of the treated organism. Thus, metabolic anomalies, e.g. hypoglycemic conditions, which are the result of decreased glucose concns. in the blood., are prevented and/or ameliorated. The method of the invention represents a new approach for increasing endogenous blood glucose concn. It is simple, and com. useful. The effect of DPIV inhibitor **isoleucyl thiazolidide** is presented.
AN 132:117551 CA
TI Procedure for the increase of the blood glucose level in mammals
IN Demuth, Hans-Ulrich; Hoffmann, Torsten; Kuhn-Wache, Kerstin; Rosche, Fred
PA Probiodrug Gesellschaft fur Arzneimittelforschung m.b.H., Germany
SO Ger. Offen., 8 pp.
CODEN: GWXXBX
DT Patent
LA German

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19834591	A1	20000203	DE 1998-19834591	19980731
	EP 995440	A1	20000426	EP 1999-115236	19990802
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	US 6319893	B1	20011120	US 1999-365404	19990802
	US 2002071838	A1	20020613	US 2001-682968	20011102
PRAI	DE 1998-19834591	A	19980731		
	US 1999-365404	A3	19990802		

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
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